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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,539	09/19/2005	Etsuro Ono	HER0071	5349

832 7590 09/05/2008

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
09/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,539	ONO ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 23, 2008, and the amendment filed January 25, 2008, that includes a response to the final office action dated July 25, 2007, have been entered. Claims 1-13 have been cancelled, and claims 14-27 newly added. Accordingly, claims14-27 are pending in the application

Claims 14-27 are currently under examination.

Response to Objection to the Specification

The specification was objected in the previous office action dated July 25, 2007, as devoid of a brief description of the drawing figure(s). Applicants have provided a description of Figures 1-6. Thus, the previous objection is hereby withdrawn.

Response to Claim Objections

Claims 2-9 were previously objected to in the office action dated July 25, 2007, as constituting improper dependent claims. In view of Applicants' cancellation of the claims, rendering the objection moot, the previous objection is hereby withdrawn.

Response and New Claim Rejections - 35 USC § 112- Second Paragraph

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 2, 3 and 5-9 and 10-13 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite, in the previous office action dated July 25, 2007. Applicants' cancellation of the claims renders their rejections moot. Thus, the previous rejections are hereby withdrawn.

Claims 14-16, 24, 25 and 27 are newly rejected as being indefinite. Claim 14 is unclear. The claim recites constructing a transgene including "optional targeting sequences". The nature of said the targeting sequences remains unclear, as a targeting may be any of numerous intracellular or extracellular targets, or homologous regions in the genome.

Claim 24 is unclear. The claim recites "germplasm essentially derived from said mammal". While the germplasm may be derived from the mammal, it is unclear what source other than the mammal may be used. Deleting the word "essentially" would obviate the rejection.

Claim 25 is unclear in reciting the limitation: "wherein said introduced recombinant DNA expresses said polypeptide"; because it is not clear how transgene expression may take place in the absence of an operably linked promoter.

Claims 15, 16 and 27 depend from claim 14, and are therefore included in the rejection.

New Claim Rejections - 35 USC § 112- New Matter

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claim 14-27 are newly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art (hereafter the Artisan), that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR §1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Claim 14 is directed to a process for producing a mouse, pig or cattle resistant to infection by PRV (pseudorabies) or BHV-1 (bovine herpesvirus) viruses, comprising constructing a transgene including the at least the "coding sequence of a fusion protein of the V domain or the VCC domain of porcine or bovine nectin-1 and the crystallisable fragment of an

immunoglobulin selected from the group consisting of human, porcine, bovine, or mouse immunoglobulin operably linked to a promoter and regulatory sequences and optional targeting sequences and selectable markers". The instant specification is devoid of such description regarding "the V domain or VCC domain of bovine nectin-1", the Fc fragment of "bovine or mouse immunoglobulin", and "optional targeting sequences and selectable markers". Claim 16 additionally recites "wherein one or both of said nectin-1 or said immunoglobulin belong to a homologous species of said mammal". Claim 25 also recites "the V domain or the VCC domain of porcine or bovine nectin-1 linked or fused to a crystallisable fragment of an immunoglobulin selected from the group consisting of human, porcine, bovine, or mouse immunoglobulin".

Applicants state that the specification (p. 6, lines 24 to 37) discloses a fusion of comprising the extracellular domain of porcine HveC protein. In particular, the production of a fusion protein having an extra-cellular domain of the porcine receptor HveC that binds to the PRV virus and the crystallisable portion Fc of the human immunoglobulin IgG-1; further stating that the inventors contemplated production of a transgene encoding a fusion protein of the extracellular domain of porcine or bovine HveC or nectin-1 and the crystallisable portion Fc of the mammalian IgG-1, for example, p. 10, lines 21-26. Such is not found persuasive, because the cited parts of the specification fail to disclose either explicitly or implicitly, the specific combinations of the nectin-1 and Ig domains from the species of mammals specifically claimed. The instant specification discloses only the porcine V and VCC domains (HveC domain) of nectin-1 fused to the Fc fragment of human or pig (Figure 6; for example).

Thus, at the time the application was filed, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of "the V domain or VCC domain of bovine nectin-1", the Fc fragment of "bovine or mouse immunoglobulin", the nectin-1 and immunoglobulin domains of "a homologous species", and "optional targeting sequences and selectable markers", as claimed.

MPEP 2163.06 notes: "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was

filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure".

This is a new matter rejection.

Response & New Claim Rejections - 35 USC § 112 – Written Description

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 2, 3 and 5-9 and 10-13 were rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, in the previous office action dated July 25, 2007. Applicants' cancellation of the claims renders their rejections moot. The ground of rejection set forth on pp. 5-7 of the office action dated November 1, 2006 and pp. 3-4 of the previous office action dated July 25, 2007 is applied to newly added claims 14-27 for reasons of record.

Applicants disagree with the rejection, arguing that the claims have been amended and directed to mammals selected from the group consisting of mice, pigs, and cattle and to be directed to the VCC and V domains of nectin-1. Further arguing the polypeptide sequence of nectin-1 is remarkably well conserved between the mouse, porcine and bovine species of mammals, which provides a reasonable basis for assuming a significant structural and functional identity between the chimeric proteins in these species, citing Milne, et al., Virology, 281, 315-328 (2001), showing a 97% amino acid identity of the HveC extracellular domains for pigs and cows, and a 93% identity between mice and pigs and cows.

Applicants' arguments have been fully considered, but are not found persuasive. In response, it should be noted that instant base claim are directed to producing a mammal that is a mouse, pig or cattle, and the latter is not limited to a cow or bovine. Moreover, the process requires a fusion protein between the V or VCC domains or nectin-1 and the Ig Fc fragment from

a number of species including bovine, for which possession has not been demonstrated. Dependent claim 16 additionally requires further combinations of the fusion proteins form homologous species. In addition base claim 17 encompasses any mammalian species produced by the various VCC, Fc combinations of fusion proteins. As such, the structure/function relationships of the various species combinations remains unknown, as the claims encompass the V and VCC extracellular domains of nectin-1, that would further retain an ability to confer resistance to an infection by any PRV or BHV-1 viruses.

As previously indicated, the specification only discloses the chimeric proteins containing the extracellular domain of Hvem (specifically, the mouse and porcine HveC) fused to the Fc portion of the human immunoglobulin IgG-1, introduced into the fertilized mouse embryo pronuclei (pp. 11 and 16), but does not describe the structure or functional nature of any chimeric proteins containing parts or sub-parts of nectin-1 or HveC from numerous species of animals that would include peptides yet to be discovered. Because the instant specification is silent on which parts of nectin-1 from the numerous species of mammals claimed would retain such an activity, possession of the numerous species has not been demonstrated at the time of the invention. Thus it is maintained that the written description requirement is not satisfied for the claimed genus of fusion proteins or mammals.

Response & New Claim Rejections - 35 USC § 112- Enablement

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 2, 3 and 5-9 and 10-13 were rejected under 35 U.S.C.§112, first paragraph, as failing to comply with the enablement requirement, in the previous office action dated July 25, 2007. Applicants' cancellation of the claims renders their rejections moot. The rejection set forth on pp. 7-11 of the office action dated November 1, 2006 and pp. 4-7 of the previous office action dated July 25, 2007 is maintained in modified form, and applied in part to newly added claims 14-27 for reasons of record.

Claims 14-27, while being enabling for a process for producing a mouse resistant to infection by PRV, whose genome comprises a transgene recombinant DNA including the coding

sequence of a fusion protein of the VCC domain of porcine nectin-1 and the crystallisable fragment of an immunoglobulin selected from the group consisting of human or porcine immunoglobulin operably linked to a promoter, does not reasonably provide an enablement for a process for producing mice, pig and cattle (or any non-human species of mammal) resistant to infection by PRV or BHV-1, whose genome comprises a fusion protein of the V or VCC domains of porcine, bovine or homologous species of non-human mammal, and the crystallisable fragment of an immunoglobulin selected from the group consisting of human, porcine, bovine or mouse immunoglobulin operably linked to a promoter, produced by targeted homologous recombination to an undefined genomic locus, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants disagree with the rejection, arguing that the amended claims are now limited to pigs, cattle and mice and to chimeric proteins including the VCC or V domains of porcine or bovine nectin-1. In addition, nuclear transfer gene introduction by homologous recombination is extensively documented in mice and in pigs and cattle, citing various articles. Applicants' arguments have been fully considered, but are not found persuasive.

The instant claims encompass the production of transgenic animals by introducing a transgene DNA into pronuclei of fertilized zygotes by pronuclear microinjection or into cultured cells and targeted incorporation of said transgene DNA in an undefined target location by homologous recombination. The fact that a given construct may react differently from one species to another, or on the particular chromosomal integration site remains unchanged. Moreover, the transgenic mice described in the instant specification were not generated by homologous recombination to a particular chromosomal locus. The specification fails to direct an artisan of skill to target the transgene to a specific chromosomal location in the genome of the claimed mammals. The specification states that infection mediator abilities of HveC in relation to the entry of the targeted virus, so as to ultimately inhibit the entry of this virus into the cell and favor its elimination, is by a process which is still to be determined (p. 7). Further, the post-filing art of Crusio (Biol. Psychiatry 56:381-385; 2004), demonstrates that genetically manipulated mice show flanking and genetic background problems, or complications due to linkage and epistasis, with closely linked genes flanking the targeted locus effecting phenotype (Title and

Abstract). The genetic background effect on the introduced mutation can occur regardless of whether the loci are linked or localized on completely different chromosomes (second column, p. 384). Crusio states that the only solution is to test the effects of a mutation on several different clearly defined backgrounds (second column, p. 384). In the instant case, the transgenes of interest are required to provide resistance to PRV or BHV-1 viruses in pig and cattle, based on observations in a few lines of transgenic mice, that each show variations to PRV infection.

As a separate issue, the instant specification fails to demonstrate any in vivo data regarding resistance to infection by BHV-1 virus. Tables 6 and 7 present data regarding resistance to PRV virus in HveC fusion transgenic mice. Resistance to infection is clearly dependent on both the type of HveC receptor and the particular alphaherpesvirus. As the specification fails to disclose either a transgenic bovine, porcine or cattle expressing the various claimed V domain or VCC domain fusion proteins, any resistance of these transgenic animals to PRV or BHV-1 virus infections remains unknown and would have to be determined by further experimentation.

Applicants argue that transgenic pigs expressing HveC (VCC-Fc), were challenged with a single dose of PRV virus strain to qualify the efficiency of vaccines used for pigs, though the infection is not lethal to pigs. Applicants provide a table showing weight gain from day 0 to Day 19 of challenge versus controls. However, the data fail to provide any statistically significant conclusions, to obviate the grounds for rejection. Moreover, the transgenic pigs were not produced by a transgene by homologous recombination to an undefined region of the genome; and were not shown to have been rendered resistant to an infection by either PRV or BHV-1 virus.

Therefore, rejection is applied in part to newly added claims 14-27 for reasons of record and the foregoing discussion.

Response & New Claim Rejections - 35 USC § 103

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 2, 3, 5 and 10-12 were rejected under 35 U.S.C. §103(a) as being unpatentable over Fiume et al. (U.S. Patent No.: 6,469,155, filed Nov. 9, 1999), in view of Bujard et al. (US. Patent No.: 5,866,755, Feb. 2, 1999), in the previous office action dated July 25, 2007. Applicants' cancellation of the claims renders their rejections moot. The rejection set forth on pp. 12-13 of the office action dated November 1, 2006 and pp. 7-8 of the previous office action dated July 25, 2007 is applied to newly added claims 14, 15, 17, 18, 20, 23 and 25-27 for reasons of record.

Applicants traverse the rejection, argue that Fiume et al. discloses the use of nectin-1 for the purpose of "biotechnological identification and production of proteins which act as mediators of HSV in human or animal models. Further arguing that while Fiume et al. mention "transgenic mice expressing HIgR or HIgR and PRR-2, or HIgR and other mediators of HSV-1, HSV-2 and BHV-1 entry", they do not say that these animals would be expected to be resistant to herpesvirus infection; that the fusion proteins were disclosed in a different context; that the application entails a mouse model that sustains BHV-1 infection, and the usefulness of such animals implies that the transgenic animals are supposed to be susceptible to such infections, thus teaching away from the claimed invention. Applicants' arguments have been fully considered, but are not found persuasive.

As an initial matter, the previous office action incorrectly referred to Ono et al., instead of Fiume et al., in the second paragraph, p. 8. Thus, the only art rejection of record is that of Fiume et al., in view of Bujard et al.

In response, it is noted that Applicants' arguments are directed to certain embodiments of Fiume et al., while ignoring their primary teachings. The object of the Fiume patent is to utilize HIGR and related domains which bind the glycoprotein D of herpes simplex virus in preventing infection by said virus (Title and Abstract). Fiume et al. describe various fusion proteins between various segments of HIgR (herpesvirus immunoglobulin-like receptor) and the Fc portion of human IgG1 (Abstract and column 4). Specifically described are sVCC(PVRα)-Fc containing the soluble V domains of HIgR (column 4 and Example 4), in addition to the discovery in the prior art that a soluble form of HveC containing the entire ectodomain is capable of such binding (column 17). Fiume et al. further state that an object of their invention is to provide cells that are

resistant to infection by HSV-1, HSV-2 and BHV-1 (column 1). Fiume et al. state that an embodiment of their invention is the construction of transgenic mice expressing the alphaherpesvirus receptors that mediate HSV and BHV-1 entry, from transgenes to produce a mouse model system for the viral infections (column 3). Thus, utilizing domains or parts of a nectin-1 outside its physiological context, and meeting the limitations of the instant claims. The foregoing does not constitute a teaching away from Applicants' claimed invention. As previously noted, the prior art rejection has been applied only to the extent that the claims read on transgenic mice rendered resistant to an infection by PRV virus, said mice containing a transgene encoding a chimeric HveC/Fc IgG fusion protein, and a process of producing said mice.

In response to Applicants' argument that Fiume et al. disclose full-length receptor and not fusion proteins, for the purpose of increased virus susceptibility, it is again noted that such is but one embodiment of their invention, as Fiume et al. specifically describe various fusion proteins between various segments of HIgR (herpesvirus immunoglobulin-like receptor) and the Fc portion of human IgG1 (Abstract and column 4). Specifically described are sVCC(PVRα)-Fc containing the soluble V domains of HIgR (column 4 and Example 4), in addition to the discovery in the prior art that a soluble form of HveC containing the entire ectodomain is capable of such binding (column 17).

Therefore the rejection is applied newly added claims 14, 15, 17, 18, 20, 23 and 25-27 for reasons of record and the foregoing commentary.

Conclusion

Claims 14-27 are not allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
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